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Jordan J. Cohen, M.D., President

August 1, 2000

Stuart L. Nightingale, M.D.
Office of the Assistant Secretary for Planning and Evaluation
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20101

Dear Dr. Nightingale:

The Association of American Medical Colleges appreciates this opportunity to comment on the issues posed in the July 3, 2000 *Federal Register* [65 FR 41073 - 41076] that will serve as the basis of discussion at the August 15-16 HHS conference on handling conflicts of interest in human subjects research. As you are aware, the AAMC represents all 125 accredited U.S. medical schools, over 400 teaching hospitals, and approximately 90,000 medical school faculty through 91 academic and scientific societies. Our members are intensively engaged in research as a core element of their missions, and a focal point of Association efforts has been to help them uphold the highest standards in this activity. This has included the development of reports, workshops, and resources to insure the quality and integrity of clinical research specifically, as well as to deal effectively with both conflicts of interest and conflicts of commitment in research more generally.

The AAMC's longstanding views on the latter are embodied in its 1990 *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research*, produced by what was then the Association's Ad Hoc Committee on Misconduct and Conflicts of Interest in Research (copy enclosed for your reference). The Association firmly believes, as expressed in that document, that "scientists have an overriding responsibility to maintain the highest standards of objectivity and freedom from bias," and that, "incidents of scientists allowing a personal or outside interest to cloud their professional judgment in conducting research are alarming and unacceptable." In responding to the questions posed in the *Federal Register* notice, the Association will draw on these and other well-established principles set forth in that document.

Conceptualizing conflicts of interest in research

Conflicts of interest are of concern in research because they can threaten the integrity of the research process and the credibility of research results. This threat stems from the fact that research is one of a number of professional activities that demand objectivity and freedom from bias. The scientific method is therefore designed to enable objective observation and analysis, in the understanding that even the most conscientious scientists have an array of intellectual, intuitive, and other biases that can potentially prejudice them in their experimental designs; their selection, analysis, and interpretation of data; and their reporting of results. Scientists frequently approach their work with preconceived notions of how the natural world

functions, and knowingly or unconsciously may set out to prove theories that they already believe to be true. The value of the scientific method is that it helps keep these sources of bias in check through its insistence on publication and replicability, as well as the use of random sampling, blinded control groups, and other bias-avoidance techniques. In addition, our scientific system relies on peer review in funding and editorial decision making, which brings the critical eyes of others with different perspectives, interests, and biases to bear on the research design, execution, and conclusions.

In spite of the safeguards offered by the scientific method and peer review, the public, Congress, and the federal agencies have for the past two decades become especially concerned about the potential for bias and poor judgment that may be engendered by financial interests. And yet, financial interests are not the only potential source of bias in a scientist's realm, and are arguably not even the most powerful. Desire for positive publishable results, for recognition among peers, for validation of ones ideas, for success in seeking external funding, and for academic advancement can all be intensely biasing. Yet, public policy concerns have been limited to the influence of monetary interests. Is this sound? We believe so, especially in biomedical research.

First, in academic life intellectual sources of bias, although amorphous, are apparent; that is, they are generally recognized to be ubiquitous and are presumed to be manageable through normal academic and scientific processes (although these processes cannot always be entirely successful). In contrast, financial sources of bias are tangible and quantifiable, but most often inapparent until they are disclosed. That is why we as a scientific community have chosen to rest our management of financial conflicts of interest in biomedical research on the principle of full disclosure of all such interests that are deemed to be "significant" by exceeding a predetermined threshold level. Second, both the media and the lay public, which are intensely engaged with biomedical research findings, can understand and relate to financial interests and their potential for bias far better than they can to conflicting interests that are solely academic. Therefore, public trust in the biomedical research enterprise, which is critical to the viability of the enterprise, can only be sustained if financial interests are, ***and are perceived to be,*** managed in a credible way.

Discerning "relevant" financial interests

Taken together, the fundmental issue at the heart of the first set of questions posed in the *Federal Register* seems to be **what types of financial interests held by investigators, institutions, and staff are particularly germane to human subjects research?** At the risk of sounding glib, the short answer would be "any that could compromise an investigator's or administrator's judgment." In other words, the interest is germane if it could bias an academic professional's objectivity, regardless of its nature. The most commonly publicized interests of this sort for those who do human subjects research are equity positions in companies that manufacture products – particularly biologicals, drugs and medical devices – that investigators may evaluate for efficacy and safety. But these are not the only possibly relevant interests, and it would be unwise to conceptualize the issue so narrowly. Faculty may receive

substantial consulting fees, honoraria, gratuities, or special favors from commercial sponsors of their research, or lavish compensation and luxurious accommodations for relatively minor contributions to continuing medical education programs that promote sponsors' products. Alternatively, they may hold financial interests in companies that compete with the manufacturer of the product under study. So the question becomes, out of the broad menu of financial interests that investigators, IRB administrators, institutional administrators, and others may hold, how can the "significant" ones be identified while keeping the disclosure process manageable and within reasonable bounds? One means is to limit reportable interests to those that are considered to be directly germane to a given activity, e.g., financial interests in a company that sponsors an investigator's research, or in other companies in the same industry. A second means is to set a reporting threshold that defines the magnitude of interest that is sufficient to be reasonably considered as potentially biasing. These procedural issues are elaborated on later in this letter.

Implicit in the brief discussion above is the absolutely critical need for case-by-case decision-making in dealing with conflicts of interest. The very same scenario may present a potential source of bias in one instance but not in another, depending on the nature of the research, the particular financial interests, and the kinds of controls that are in place. This was recognized by the PHS, NSF, and FDA in their approaches to dealing with this issue, which allow institutions or sponsors (in the case of FDA) to conduct case-by-case evaluations within the parameters of general requirements, such as thresholds.

IRB and Institutional Conflicts of Interest

Imbedded in many of the questions posed are concerns about conflicts that IRBs and institutions may have. IRB conflicts are not dissimilar from those created by the financial interests of investigators and may thus be handled similarly. IRB members should be instructed to report any interest germane to a protocol under review that might perceivably cloud their judgment in evaluating that protocol fairly. In addition to financial interests, IRB members should also be mindful of any other activities or interests that might be biasing, such as recent or ongoing collaborations with the scientist proposing a research activity, financial interests in the company sponsoring a proposed trial (or in a competitor), and even familial relationships. These interests should be disclosed and evaluated, and IRB members should assume the responsibility to recuse themselves from participating in the review of that protocol if they cannot be objective.

Institutional conflicts of interest are another source of bias often discussed, but not often well characterized. Institutions become vested in other entities through equity positions and major collaborations, and in recent years, some institutions have become investors with faculty in start-up companies founded on those faculty members' inventions (a practice discouraged by many leaders in the academic community).

These kinds of situations and interests occur routinely in industry, where the institutional financial interest in research is direct and obvious, as is the stake of employee researchers in

the outcome of their activities. But academic institutions are traditionally the arbiters of independent knowledge, a role that the public expects them to uphold. They have a different relationship to their faculty and students than occurs in a private company. Faculty are independent thinkers, and there is a constant tension between allowing freedom of academic activity while exerting appropriate institutional oversight.

That said, there are potent incentives for institutions to handle compliance and oversight activities appropriately, including conflicts of interest. The impact of problems when they arise can be punishing to the institution and involve major financial costs, both civil and criminal liability, and an often-unrecoverable loss of reputation. The driving effect of these forces on institutional decision making is tremendous indeed.

In addition, individual awareness of institutional investment portfolios is generally quite limited, and thus most faculty and administrators overseeing human subjects research will not have sufficient personal knowledge to allow institutional financial considerations to impede their judgment. To the extent such knowledge does exist, individuals will have significant incentive to make decisions that preserve their professional credibility and protect them from personal liability. Finally, it is plainly a dangerous and foolhardy business strategy for any entity, private or public, to compromise the integrity of the activities that are at the core of its mission by allowing corporate financial interests to undermine its compliance obligations.

Thus, the question of institutional conflicts of interest may be less germane to the protection of human subjects than pure managerial resolve to handle this and other compliance matters rigorously and with attention to detail. Widely publicized reports of failures in institutional regulatory compliance have stemmed almost entirely from inadequate surveillance, education, oversight, and policy implementation, and not from institutional behaviors that satisfy any particular investment interest on the part of the medical school or university.

Furthermore, resolve must accompanied by resources and good judgment. The best way to handle many conflict-of-interest situations will not be obvious and, at the institutional level, managers will have to ask themselves whether disclosure of financial interests suffices in protecting human subjects and the integrity of the research itself. And they must question whether there are circumstances in which the conflict cannot be "cured" by disclosure alone.

Also, institutional leaders must question the appropriateness, from a public perception point of view, if none other, of becoming sponsors of clinical trials of products produced by companies in which they have a major, even controlling, investment positions. Or whether faculty should ever be principal investigators on trials of products produced by companies in which their institutions hold significant financial interests. If they go down those roads, they must create the oversight and safeguards that will not only protect the well being of human subjects and the integrity of the research, but that will also withstand public scrutiny.

Disclosure in human subjects research

The next set of questions posed by the Department addresses the issue of **how disclosure should be made in the context of human subjects research, with particular regard to the risks and benefits to human subjects, informed consent, and the objectivity of the research activity**. In particular, HHS seems interested in empirical evidence or documentation of the impact of such disclosure on the research. To the AAMC's knowledge, there is no significant body of literature on these specific matters, and embarking into such an area of investigation in a credible way would be extremely difficult. This is due to the complexity of the issue, given the diversity of interests and individuals typically involved. Investigators, administrators, and institutions all have multiple interests that can potentially create conflicts, and equally numerous ways in which conflicts can be managed when they occur. These variable circumstances then have to be arrayed against the extremely diverse types of potential human subjects (including their highly variable ability to process and factor disclosure information into their judgments about participation in research), and the heterogeneous nature of research protocols and the levels of risk they may carry.

Adding a third dimension of complexity to the issue is timing, which the *Federal Register* notice does not fully explore. Clearly, the means by which to handle disclosure properly will vary according to the stage of the research process. When proposing research, investigators have a responsibility to report any known conflicts to the institution, so that the institution can determine how they should be managed or eliminated. In some cases, the investigator may be asked to liquidate an asset before proceeding with the protocol, from which point forward that interest becomes moot, and no further disclosure is necessary. In another scenario the institution determines that the disclosed interest is irrelevant to the project at hand, or so insignificant as to hold no potential for creating bias. If so, then further disclosure would also seem unnecessary.

If the interest is deemed relevant but nonetheless permitted by the institution, it is usually because a way has been found to manage the interest and even monitor the project so as to minimize the opportunity for bias. In this instance, the AAMC generally supports full public disclosure. In the early stages of research, this should include informing the IRB, as well as prospective subjects (or their legally designated representatives) to the extent that the IRB judges it within the patients' interest and capacity to be informed. Later in the research process, disclosure should be made in all public presentations of scientific findings -- be it through published papers, poster sessions, formal lectures, or contacts with the media. Such disclosure should also address the means by which the potentially biasing influence of the interest in question has been managed.

It should be noted that a number of organizations, including the AAMC, have developed guidelines and standards of conduct that reinforce this concept of disclosure. The aforementioned *Guidelines* on faculty conflicts in research state that

> Full disclosure of relevant information is in the best interest of both the institution and the faculty member. It demonstrates good faith on the part of the investigator and protects his or her reputation and that of the university or hospital. Disclosure will not necessarily restrict or preclude an investigator's activities. In fact, activities that might be veiled in a cloud of suspicion and doubt may be found acceptable and permissible when all facts regarding the activity are brought to light a priori.

The *Guidelines* go on to say that

> General awareness (institutional or public) of an investigator's relevant funding sources, financial interests, and professional roles, serve to direct appropriate scrutiny at elements of research commitment, design, and reporting of data that might be biased or undermined by these factors. The investigator's cognizance of that scrutiny further encourages vigilance to avoid any biases or diversions that inadvertently may be introduced. Naturally, for this system to work, the disclosure process must insure that information regarding possible conflicts reaches all individuals with an appropriate interest in evaluating the research in question.

These concepts are also reinforced in the AAMC's 1992 *Guidelines for Faculty Involvement in Commercially Supported Continuing Medical Education*. Although this document outlines appropriate conduct for individuals involved in CME activities, the principles that it espouses are applicable elsewhere. This document urges CME faculty to:

- disclose fully and specifically to the CME course coordinator and sponsor those professional and relevant personal activities, paid or otherwise, that may bias one's presentation, and to

- avoid participating in a CME program if being retained as a consultant by the grantor organization or a competitor, or having any managerial or equity interest, or benefiting through sponsorship of one's research by that organization or a competitor, unless such affiliation is fully disclosed to the sponsor and audience.

The *Federal Register* notice asks a series of questions concerning **what type of information should be disclosed to research participants, and what level of detail.** The guiding principle should be to disclose financial interests that (a) are relevant to the research activity, (b) are in the patient's interest to know, and (c) whose disclosure would be beneficial to the research activity in general. So, for example, the IRB must determine whether knowledge of a given financial interest would allow patients to make better judgments about the research in which they are contemplating participation. Even if this is not the case, the IRB might consider whether inadvertent disclosure during or after the protocol would be so harmful to the

relationship of trust between the patient and the investigator that *a priori* disclosure is the best course of action.

Clearly, there is no justifiable reason to disclose to patients all the financial interests held by an investigator (one of the possibilities raised in the notice), which would constitute an unwarranted invasion of privacy. It could also have an adverse impact on the scientific activity by unnecessarily alarming patients and thereby impeding patient recruitment. If different kinds of patients respond differentially to such information, then the profile of consenting subjects may become skewed, frustrating efforts to create a representative, unbiased sample. Thus, the impact on the patient and the integrity of the research must both factor into the IRB's calculus.

The notice asks specifically whether the thresholds in the PHS regulations are still appropriate for clinical researchers. Lacking from this question is any context. For the purposes of federal regulatory compliance, the AAMC believes this to be true and reiterates its long-held position that threshold and other requirements should be as consistent as possible across agencies. However, when it comes to institutional decisions about what to disclose to patients, determinations about reporting thresholds must be carefully and thoughtfully made in consultation with or by the IRB. There may be justification in a given case for disclosure either beneath or above the thresholds PHS has set forth, or for no disclosure at all, depending on the value of such knowledge, the vulnerability and comprehension of the patient populations involved, and the specific design of the research protocol.

**The specific means by which information on financial interests should be conveyed to research participants**, another issue explicitly raised in the *Federal Register* notice is largely case-specific, and, once again, the IRB has a determinant role to play. The IRB acts with the patient's best interests at heart and can determine the most appropriate means for conveying such disclosure if deemed necessary. Informed consent is the usually accepted means by which to convey to potential research participants information about the activity for which they may volunteer, but an IRB may determine that because of the nature of the protocol, there are other, more appropriate means.

Oversight of possible conflicts of interest

**As for the roles of institutions, the IRB, and investigators in dealing with possible conflicts of interest**, each has a responsibility. Fundamentally, dealing with conflicts of interest must begin at the level of the individual, and in stating this, the AAMC believes that the vast majority of investigators are earnest, honest, and ethical, and seek to adhere to principles of professionalism as they understand them. A sociopath who is intent on deception and on defeating the system will probably succeed, at least to a limited degree, no matter what controls are in place. Such individuals must be dealt with through mechanisms designed to deal with deliberate and improper conduct. These mechanisms must be procedurally distinct from those that address inadvertent conflicts of interest or the possible introduction of unwanted bias.

Honest scientists must be sensitive to the potential for conflict of interest and must monitor their own behavior. Self-elimination from a potentially conflicting activity may be key to self-regulation. Some investigators have voluntarily announced that they will not buy, sell, or hold stock or stock options in any companies providing or distributing products under study. This was done by Bernadine Healy, M.D., and her research team in their study of post coronary-artery-bypass-graft surgery at the Cleveland Clinic over a decade ago[1]. They imposed this restriction beginning with the recruitment of patients until the time that the study results were made public.

On the other hand, federal research dollars are awarded to institutions, which bear ultimate responsibility for their stewardship, and, therefore, institutional controls, policies and processes are obligatory. Institutions, however, are highly complex and extremely diverse, and whatever systems are set up to control conflicts must take this variability into account. It is for this reason that there is no singularly correct procedure for handling conflicts of interest. In 1989, the AAMC solicited from its members examples of policies they had developed for handling conflicts of both interest and commitment for the purposes of developing our aforementioned *Guidelines*. In conducting a content analysis, this variability became quickly evident. Nonetheless, the basic components of a sound institutional policy emerged, and these included[2]:

1. Explicit definition of conflict of interest, often illustrated with examples,
2. Clearly defined scope of policy (e.g., affected individuals and institutions),
3. Effective procedural elements
   - Timely disclosure of relevant information
   - Thorough review of disclosed information
   - Mechanism for management and/or resolution of conflict situations
4. Sanctions for policy violations.

The HHS is presently concerned in particular about clinical research and the role of IRBs. The mission of IRBs is to protect the welfare of human subjects, and in our current system of research, we have entrusted the IRB to make appropriate judgments about the kinds of information prospective research participants have a right or need to know when making decisions about becoming part of a clinical study (as part of the process of informed consent). The question of investigator financial interests should be handled by IRBs in this context in accordance with overarching institutional policies, and in coordination with other institutional offices and functions that play a role in the oversight of potential conflicts of interest.

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[1] New England Journal of Medicine, 320 (14); 951.

[2] These elements and the pros and cons of various approaches are described in Chapter 10 of *Biomedical Research: Collaboration and Conflict of Interest*, Johns Hopkins University Press, 1992.

Before concluding, I will briefly address the matter **of what kinds of protections to ensure objectivity can be offered outside the federal realm**, the final matter raised in the *Federal Register* notice. As amply discussed above, these are largely institutional and individual in nature; but other entities can also play a role.

The first is professional and scientific societies. These organizations can do much to encourage responsible research behavior and to promote public confidence in the research enterprise by defining standards of appropriate conduct for their members. Apart from strengthening members' sense of professional identity and responsibility, codes of ethics have an educational benefit by encouraging society members to reflect upon and openly debate the complexities of responsible research practice. Society codes can also help institutions ensure the quality and integrity of their research programs by establishing norms of behavior.

In recognition of this, the AAMC produced in 1997 a resource document titled *Developing a Code of Ethics in Research: A Guide for Scientific Societies*, which lays out the issues that might be addressed in codes, including specifically the question of conflicts of interest. Some societies, including the American Society for Genetic Medicine, have issued firm statements to their members about these matters, taking a hard stance and a strong leadership role.

Journals are another obvious entity with an interest in this issue and that can influence the behavior of investigators. The *New England Journal of Medicine* has been a leader in developing and publicizing strict disclosure requirements for its authors and commentators. But even this Journal has run into difficulties in enforcing its own policies, a sobering fact that to us reflects the pervasiveness and intensity of academic – commercial relationships that have arisen in academic medicine.

Conclusions

In closing, I shall reinforce a few points in this letter.

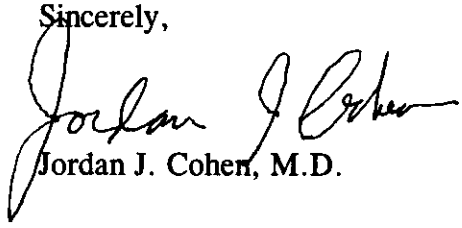
First, identifying and managing conflicts of interest are extremely complex matters that cannot be entirely handled through pat prohibitions or simple and universally applied thresholds. The federal agencies in working on both the PHS and NSF policies came to recognize this after many years of deliberations, and thus left much of the responsibility to institutions to handle in a case-specific manner.

Second, having a conflict of interest is not an act of professional misconduct. There is a tendency in the media and elsewhere to regard such conflicts as inherently scandalous, when in fact they are ubiquitous and a fact of professional life. Physicians, researchers, lawyers, and other professionals – even journalists - almost all find themselves facing conflicts of interest at many points in their careers. The key to resolution of those conflicts is to exercise integrity, use good judgment, manage the conflicts effectively, and disclose them where appropriate.

Third, IRBs have a very specific mission, and their involvement in overseeing and handling conflicts of interest must be considered accordingly. As entities designed to ensure that research subjects are not exposed to undue risk, they must evaluate an investigator's financial interest in this narrow context. In our current system of research oversight, we have entrusted the IRB to make appropriate judgments about the kinds of information potential research participants have a right or need to know when making decisions about becoming part of a clinical study. The question of investigator financial interests should be handled in the same manner.

I thank you for soliciting our views on this matter. At the August 15-16 meeting, they will be elaborated upon by AAMC Senior Vice President for Biomedical and Health Sciences Research, David Korn, M.D. I encourage you to contact Dr. Korn, or Allan Shipp on his staff, at (202) 828-0484 if you need any clarification or additional information.

Sincerely,



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